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Review

Bisphenol A: A Concise Review of Literature and a Discussion of Health and Regulatory Implications

UMAR WAZIR[1,2] and KEFAH MOKBEL[1]

[1]*The London Breast Institute, Princess Grace Hospital, London, U.K.;*
[2]*Department of General Surgery, Khyber Teaching Hospital, Peshawar, Pakistan*

Abstract. *Background/Aim: Bisphenol A (BPA) is a ubiquitous substance found in a wide array of consumer products and healthcare consumables, and at low doses in drinking water. Currently, in the UK, it is classed as a low-risk substance with little potential for harm. It has been known to have effects on oestrogen receptors. The implications of this for public safety is currently subject to debate. Materials and Methods: In this study, we review recent literature regarding the effects and safety of BPA, and discuss the potential implications, in particular from the perspective of human breast oncogenesis. Results and Conclusion: Recent evidence suggests that low-doses of endocrine disruptors, such as BPA, could have profound effects in breast development and cancer risk. Recent studies in murine models suggest that BPA could contribute to breast oncogenesis via several pathways. The position of regulators should shift accordingly to safeguard the public interest.*

Bisphenol A (BPA) is a near-ubiquitous substance in today's world. It is widely used for manufacturing epoxy resins, which are found in the protective lining of plastic food containers, healthcare equipment, steel drums and pipes. BPA is a food contact material, and is thus practically ubiquitous in household kitchenware and in canned food items. BPA-based epoxy resins are also widely used for their adhesive properties (1).

BPA is also important in the production of polycarbonate plastics, and is thus found in eye-ware, optical devices and medical equipment. BPA is also an additive in the manufacture of polyvinyl chloride plastics, which have wide applications in healthcare consumables, piping, wire insulation and construction materials (1, 2).

The annual world production of BPA in 2009 was at least 2.2 million tonnes, with the USA producing a fifth of the total (1). BPA was discovered on 1891, and has been in mass production since at least the interwar era (3). Consequently, BPA has permeated our ecosystem, making human exposure to BPA near-universal. Calafat *et al*. have found that 93% of Americans above the age of six had detectable levels of BPA in their urine (4). Arnold *et al*. have found the maximum quantified BPA concentration in European drinking water to be 0.014 μg/l. They also observed that the exposure levels were well below the stated toxic thresholds for BPA (5). This coincides with the current position of the Food and Safety Agency (FSA) of the UK (6).

Endocrine Disrupting Chemicals

The endocrine effects of BPA have been known since the 1930s. In comparison to other substances studied at the time, the affinity of BPA to oestrogen receptor was relatively weak. Unlike, for instance, diethylstilbestrol (DES), BPA was never found to have a commercial role as a synthetic oestrogen (3). However, since the 1980s, there have been concerns regarding the endocrine effects of BPA, especially since the ban of DES in 1979, after it was implicated in the causation of uterine tumours in young women who were exposed *in utero* to DES (7). The studies on DES identified molecules with endocrine effects to be of specific interest regarding oncogenesis. BPA has been evaluated as one such endocrine disruptor chemical (EDC) (8). In a commentary on reviews on the effect of BPA at the toxic thresholds recognised at the time, vom Saal *et al*. observed that the majority of studies they reviewed were showing effects due to BPA at concentrations significantly below the stated safety threshold (9). Furthermore, they noted that there was a discernible effect of funding source on the results of these studies. More than 90% of government-funded

Correspondence to: Prof. Kefah Mokbel, London Breast Institute, the Princess Grace Hospital, 45 Nottingham Place, London W1U 5NY, U.K. e-mail: kefahmokbel@hotmail.com

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studies were showing BPA to have effects at a low dose, while industry-funded studies were showing no effects (9).

Low-dose Toxicity

Since then, there have been multiple studies regarding the effects of BPA. In a review of murine studies, Wang *et al.* have found a preponderance of evidence for BPA as a potential causative agent for breast, uterine, ovarian, liver, testes, and prostate cancers at toxic doses. However, they also collated a significant body of studies showing potential effect on breast oncogenesis at low doses (<25 μg/kg/day) (10). This is consistent with the findings of Vandenburg *et al.* of a dose-dependent response of mammary budding to xeno-oestrogens in murine models. Specifically, they have found that low to moderate doses of oestrogens induced duct and bud growth in murine breast tissue, while this was inhibited at higher doses (11).

In recent *in vitro* studies by Williams *et al.*, breast cancer cell lines were exposed to low levels of EDCs, including BPA. These levels were intended to simulate exposure due to environmental contamination. The cell lines incubated with low doses of BPA exhibited increased mRNA expression of aromatase, increased synthesis of 17β-estradiol, and increased proliferation of oestrogen receptor (ER) positive cells (12).

Furthermore, Sprague *et al.* have found a positive association between serum BPA levels and mammographic breast density in post-menopausal women. They found that mammographic breast density increased from 12% to 17% when serum BPA levels increased from undetectable to 0.55 ng/ml (13). This has significant implications for cancer risk, as mammographic breast density is an independent predictor of breast cancer risk (14). A 5 percent increase of density, as reported in relation to BPA exposure, is believed to increase the risk of breast cancer by 5-10% (15).

Similar findings were reported by Binder *et al.*, who found a positive association between urinary levels of EDCs and mammographic breast density in adolescent females, with a difference in mammographic breast density of 7% seen between patients with the highest and lowest urinary levels of EDCs. The authors speculated that these effects may impact breast cancer risk later on in life (16).

These findings are in keeping with the observation that exposure to environmental stimuli at key points of human development could increase the risk of various pathologies later in life, including cancer(17). Pertinent to human breast cancer, exposure to radiation or EDCs during puberty, in pregnancy or *in utero* is believed to increase the risk of developing breast cancer later on in life. This risk has been better characterised in the case of DES, in which *in utero* exposure had led to higher risk of several neoplastic diseases, including breast cancer (17, 18).

In the absence of adequately powered epidemiological studies, evidence derived from *in vitro* and *in vivo* studies and human studies using surrogate markers for breast cancer such as breast density become critical. These findings make the low but ubiquitous ambient exposure to EDCs such as BPA all the more a cause for concern. Additionally, recent studies have posited that BPA may induce oncogenic pathways other than those related to hormone receptors, including those pertaining to stem cell differentiation (19), DNA repair (20), and immunomodulation (21).

Furthermore, it has been found that despite its limited half-life, BPA accumulates in adipose tissue in its active unconjugated form (13, 22). This could serve as a continuous source of exposure in humans, which cannot be effectively modelled for in murine models. It is not unreasonable to expect that exposure to and effects of BPA will be worse than that predicted by murine studies (4).

This accumulation of evidence has led to mounting concerns at the market and regulatory level. BPA-free products are currently being offered (2), and certain regulators have revised their previous rulings regarding BPA. A full ban was considered in France (23). Most recently, the US National Toxicology Programme has concluded its study on the effects of BPA, and shall be publishing their final report in the fall of 2019 (24).

Safer alternatives to BPA have been developed. For example, syringaresinol has been characterised as a renewable and safer alternative to BPA in the manufacturing of epoxy resins. Such alternatives make the phasing out of BPA from consumer goods feasible (25).

Conclusion

In view of the developments in our understanding of the effects of low-dose xeno-oestrogens, it is imperative that measures should be taken to curb further cancer risk to our populations. BPA, and indeed other EDCs, should be phased out as soon as feasible. The full extent of their effects is difficult to predict, and what we have determined is highly suggestive of an increased risk of human oncogenesis, including breast cancer. It would be imperative to phase out BPA from use in the manufacture of consumer and healthcare goods in favour of safer alternatives (25).

Conflicts of Interest

UW and KM declare that they have no conflicts of interest regarding this study.

Authors' Contributions

KM initiated the project. UW did the literature review and drafted the initial manuscript. KM proof-read and finalised the manuscript.

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